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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/052,092	01/18/2002	Suzanne Fuqua	HO-P02102US2	5838

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EXAMINER

SWITZER, JULIET CAROLINE

ART UNIT PAPER NUMBER

1634

DATE MAILED: 01/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/052,092	FUQUA ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 December 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 3-10, 12-14, 16-20, 22, 64 and 65 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 5-9 is/are allowed.
- 6) ☒ Claim(s) 3, 4, 10, 12-14, 16-20, 22, 64 and 65 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
 * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
 a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413) Paper No(s). <u>0104</u> . |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>12-16-03</u> . | 6) <input type="checkbox"/> Other: |

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 12/16/03. Claims 5, 6, have been amended, claims 1-2, 11, 15, 21, and 23-63 have been canceled, and claims 64-65 have been added. Claims 3-10, 12-14, 16-20, 22, and 64-65 are pending and examined herein. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 12/16/03 was filed after the mailing date of the first office action on the merits on 7/1/03. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

3. It is noted that applicant states that the submitted 1449 contains the proper citation for the CB1 reference by McDonnell *et al.* However, upon review of the 1449 filed 12/16/03 it is evident that there is no citation on this 1449 by McDonnell *et al.*, only a citation by Deng *et al.* and Fuqua *et al.*

Drawings

4. The drawings are approved for examination.

Claim Rejections - 35 USC § 112-New Matter

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

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pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 64 and 65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In the instantly rejected claims, the new limitation of "female animal" in claim 64 appears to represent new matter. This limitation in the newly added claim is sufficiently broad so as to encompass any species of "female animal" that undergoes menopause, including, for example primates or elephants, which have post-reproductive phases similar to human menopause. There is no discussion in the specification of the relationship between the A908G mutation in the estrogen receptor gene and breast cancer in any animal besides a human. Indeed, there is no discussion that the mutation is even present in additional species of animals, let alone that the mutation is indicative of a risk for breast cancer in other species of animals. No specific basis for this limitation was identified in the specification, nor did a review of the specification by the examiner find any basis for the limitation. Since no basis has been identified, the claims are rejected as incorporating new matter.

Claim Rejections - 35 USC § 112-Scope of Enablement

6. Claims 3, 4, 10, 12, 13, 14, 16, 17, 18, 19, 20, 64, and 65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for

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determining a predisposition to the development of breast cancer or invasive breast cancer, wherein the presence of an A908G mutation in the nucleic acid sequence for an estrogen receptor alpha is indicative of a predisposition to developing breast cancer or invasive breast, does not reasonably provide enablement for methods of diagnosis of breast cancer or methods of classifying breast cancer in an individual. Furthermore, with regard to claims 64 and 65, the specification does not enable any person skilled in the art to identify any postmenopausal animal at risk for developing breast cancer other than a human. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Breadth of the Claims

The rejected claims each recited method steps which set forth that the presence of an A908G mutation in an estrogen receptor alpha nucleic acid sequence is indicative of the presence of breast cancer or invasive breast cancer, in particular. That is, the claims lead the practitioner to draw the conclusion that breast cancer, or invasive breast cancer in particular, is present when the particular mutation is present.

With regard to newly added claims 64 and 65, the subject of these claims is recited as a “postmenopausal female animal” which encompasses the screening of any animal that experiences menopause, including, for example, non-human primates or elephants.

State of the Art

Fuqua *et al.* (Cancer Research 60, 4026-4029) reports an A to G transition at nucleotide 908 of the estrogen receptor alpha gene, and further teaches that this alteration was found in 18 of 55 premalignant lesions (p. 4027). It is to be noted that Fuqua *et al.* have some authors in

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common with the inventors of the instant application but have a different inventive entity per se. Further, the experiments presented by Fuqua *et al.* in the journal article are also presented in the examples of the instant specification. Fuqua *et al.* further teach that “hyperplasias are relatively common in the breast, and only a small fraction of them will progress to cancer (p. 4029).”

Fuqua *et al.* do not test actual breast cancer tissue for the presence of the mutation, they only test hyperplasias, which by definition are not cancer. The prior art does not teach that this mutation is present in other non-human animals, nor does the prior art provide an association between this mutation and breast cancer in other non-human animals.

Guidance and Examples in the Specification

The specification does not provided any examples which definitively support the assertions that (a) when the A908G mutation is present breast cancer is present or (b) when the mutation is present in a cancer cell invasive breast cancer is present. To the contrary, the specification provides numerous examples of cases where the mutation is present in non-cancer tissues.

The specification teaches a novel A908G mutation in the fifth exon of the estrogen receptor gene, and further teach that this mutation causes a coding change where normal type receptors have a lysine at amino acid 303 of the receptor and mutated forms have an arginine at this position. The specification teaches that the mutation is present in 34% of 59 total cell samples taken from hyperplasias of the breast, and that the mutation appeared in normal adjacent breast tissue of some of the samples tested (Example 5). Thus, the specification demonstrates that the A908G mutation is present in samples where cancer is not present, as hyperplasia tissue and adjacent normal breast tissue are in fact not cancerous tissues. Applicant has not provided

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any data or evidence that suggests that each time the A908G mutation is present the hyperplasia or adjacent normal breast tissue develops into breast cancer, or invasive breast cancer as some of the claims recite. Example 10 shows that the A908G mutation was present in 62% of invasive breast cancer samples tested, however neither this example nor any other example in the specification tests a population of non-invasive breast cancers to determine the frequency of the mutation in non-invasive breast cancers. Therefore, lacking this critical control information, it is not possible to determine if in fact the presence of the mutation in a cancer cell is a clear indicator of the presence of invasive versus non-invasive breast cancer.

The specification does not teach that this mutation is present in other non-human animals, nor does the specification provide an association between this mutation and breast cancer in other non-human animals. The specification does not discuss non-human postmenopausal subjects.

Level of Unpredictability and Level of Skill in the Art

There is no known way to predict *a priori* if a given hyperplasia or breast cancer tumor will in fact develop into a breast cancer tumor or invasive breast cancer in particular. It is thus highly unpredictable as to whether or not the A908G mutation taught herein is in fact an indication that in fact a given hyperplasia will develop into breast cancer, or that a given breast cancer will be an invasive breast cancer. Any conclusion to that effect based on the evidence in the specification is not fully supported because the specification does not provide evidence that the presence of the mutation will necessarily result in the development of invasive breast cancer. While the level of skill in the art is quite high, the unpredictability in the prior art with regard to

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the ability to conclude that a given mutation is indicative of presence of breast cancer, or invasive breast cancer is higher.

Furthermore, with regard to claims 64 and 65, it is highly unpredictable as to whether or not this mutation which has been shown to occur in humans occurs in other postmenopausal animals, and if it does whether or not it is an indicator of risk for breast cancer.

Quantity of Experimentation

In order to practice the claimed invention, the one would have to undertake many further experiments to determine what percentages of hyperplasias and related normal tissues that have the mutation do in fact develop into breast cancer and invasive breast cancer in particular. In order to practice methods of classifying cancer cells as invasive breast cancer cells, one would have to sample hundreds of patients in order to determine whether or not the A908G mutation in the estrogen receptor alpha is in fact present in non-invasive types of breast cancers. Such experiments that would be necessary to provide the critical data necessary to practice the invention would be complicated, time consuming and require the assaying of hundreds of patients.

Likewise, in order to practice the invention of claims 64 and 65, one would have to screen large samples of a variety of postmenopausal animals in order to determine if in fact the A908G mutation is present in these animals, and if it is an indicator of a predisposition to breast cancer.

Conclusion

Upon considering all of these factors, it is concluded that it would require undue experimentation to practice the claimed invention commensurate in scope with the claims.

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Namely, this conclusion is drawn due to the high level of unpredictability in the art, the lack of working examples with regard to the claimed invention, the high quantity of experimentation necessary to practice the invention, and the breadth of the claims which lead the practitioner to conclude that cancer is present in a sample or invasive breast cancer is present in a sample merely due to the presence of a mutation that has been shown to be present in non-malignant tissue as well as in malignant tissues. Furthermore, it would require inventive, undue experimentation to apply the instant invention to animals other than humans.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kimoto (GenBank Accession E13443, GI: 3252248) in view of Stratagene Catalog, 1988.

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Kimoto teaches a primer which comprises instant SEQ ID NO: 15. In particular, nucleotides 1 to 20 of instant SEQ ID NO: 15 are identical to the complement of nucleotides 1 to 20 of the primer taught by Kimoto.

Kimoto does not teach the primer in a kit.

Stratagene teaches gene characterization kits and the benefits of such kits.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have included the primer taught by Kimoto in a kit for the amplification of a portion of the estrogen receptor alpha gene. The ordinary practitioner would have been motivated to have produced such a kit because since the Stratagene catalog expressly teaches the benefits to the practitioner of kits:

“Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, pre-mixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control.”

It is noted that these claims contain a preamble which recites an intended use, however, it is also noted that this use does not confer patentable weight on the product claims since the preamble does not materially change what is present in the kit itself and thus represents an intended use of the kit (see MPEP 2111.02). Therefore, the kits of the instant claims are *prima facie* obvious over the disclosure of Kimoto in view of the Stratagene catalog.

Furthermore, it is note that the instant claims are currently drawn using open “comprising” type language, and thus this language has been interpreted to mean that the primers

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included in the claimed kits encompass primers that comprise the recited sequence, allowing for the addition of nucleotides onto the ends. However, it is noted that even if the claims were amended to limit the kit to containing a primer consisting of instant SEQ ID NO: 15, at the time the invention was made it was a matter of routine optimization to add or subtract nucleotides from the ends of known primers in order to provide functionally equivalent primers for the amplification of a target sequence.

Response to Remarks

The 112 1st paragraph scope of enablement rejection is maintained for the previously pending claims. New claims 64-65 are also included in the scope rejection. It is noted that the inclusion of claims 64-65 is to address the breadth of the claim with regard to possible subjects and that the claim does not recite a diagnostic but instead a method for determining predisposition. The following arguments address the previously rejected claims.

Applicant's arguments are addressed towards the previously pending rejection which addresses claims that recite that the presence of the A908G mutation in the estrogen receptor alpha sequence "indicates said individual has breast cancer" or "identifies said breast cancer to be invasive." Applicants assert at page 8 of the response that "they are not required to show that each and every time that the A908G mutation is present that breast cancer will develop." However, applicant is referred to the plain language of the rejected claims which each state that the presence of the mutation indicates that the individual has breast cancer or invasive breast cancer. Such a claim suggests by its very language that the presence of the mutation in a sample is sufficient to conclude that breast cancer (or invasive breast cancer) is present. The specification and prior art themselves clearly illustrate that this is not the case. Applicants state

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that “they are not claiming that the A908G mutation identifies all breast cancers, but that when the A908G mutation is present there is a susceptibility to the development of breast cancer and/or breast cancer of the individual is diagnosed thereof.” The examiner agrees that the specification supports a method which determines the susceptibility to the development of breast cancer, specifically invasive breast cancer, but for reasons stated, the examiner does not agree that the specification supports a method which recites that the presence of the mutation is indicative of the presence of breast cancer. As discussed in the rejection, applicant’s own specification and the prior art demonstrate that there are times (for example 34% of non-malignant hyperplasias examined) when the mutation is present but breast cancer is not present. Applicant suggest that the examiner is taking the specification out of context when she states that the specification provides examples of the presence of the mutation in non-cancerous tissues, and repeats paragraph 319 of the specification in the arguments, highlighting the portion of the specification which recites “in a specific embodiment a somatic mutation in ER within a localized region of normal breast epithelium defines a region of **increased risk** if the mutation confers a selective advantage to these cells (emphasis added by examiner) (p. 8-9 of arguments).” The examiner is not arguing that there is no increased risk of development of breast cancer, and the examiner agrees, as applicants argue, that the specification supports the assertion that the cells from “normal” tissue “in fact demarcate a localized region having cells predisposed to becoming cancerous.” The examiner maintains, however, that this is a different conclusion from the one which the rejected claims sets forth, which is that the presence of the mutation indicates the presence of disease. This assertion is not supported by the specification

which does demonstrate, as admitted by the arguments that the mutation is present in patients who have not developed breast cancer.

Applicant's argue at page 10 that "based on the teachings provided in the specification...the data presented in the accompanying affidavit of Dr. Suzanne Fuqua is further support that the presence of the mutation will result in the development of breast cancer (p. 10 of arguments)." However, the rejected claims state that the presence of the mutation is indicative of the presence of breast cancer. Therefore, this argument is not commensurate in scope with the rejected claims, and is not persuasive with regard to the rejected claims.

Applicants argue that there is little unpredictability to obtain a breast sample and assay it for the A908G mutation (p. 11). However, the unpredictability discussed with by the examiner is not with regard to the actual practice of the method steps, but instead in discerning what the presence of the mutation means, as previously discussed. Applicants argue that it is inaccurate to assert that many further experiments would be necessary to enable the invention, but the examiner disagrees, as further experimentation would be necessary to provide data sufficient conclude that the presence of the mutation is sufficient to conclude that breast cancer is present. Such experimentation would essentially have to contradict the experimentation provided in the instant specification which demonstrates that the mutation is present in cases where cancer is not present.

The examiner has made no requirements as that every operable species be demonstrated, however, the examiner is looking to the specification for evidence or data which supports the conclusions drawn by the plain language of the claims, which evidence is not present in the specification as filed, nor the affidavit which supports the data in the specification but does not

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support the diagnostic relationship set forth by the plain language of the claims. Thus, even in light of the affidavit and arguments, the rejection is maintained.

With regard to the prior art rejection of claim 22, applicant argues that it is certainly not taught that “a specific A908G mutation in an estrogen receptor alpha nucleic acid sequence could be diagnosed by such a kit (p. 14 of response).” However, this is irrelevant, as this language is intended use language. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In the instant case, the kits comprising primers provided in the prior art are structurally identical to the claimed kit (see MPEP 2111.02). Applicant is further reminded that “The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable (MPEP 2112).”

Conclusion

10. Claims 5-9 are allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO**


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MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached by calling (571) 272-0782.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-0507.


JEFFREY FREDMAN
PRIMARY EXAMINER


Juliet C Switzer
Examiner
Art Unit 1634

January 27, 2004